REMARKS/ARGUMENTS

Claims 36-49 are currently pending in the instant application. All pending claims stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled by the specification. In view of the remarks and arguments set forth hereinbelow, and the Declaration of Dr. Jamey Marth under 37 C.F.R. § 1.132, submitted herewith, reconsideration and withdrawal of the rejection are respectfully requested.

In response to Applicants' reply of February 17, 2005, to the Final Office Action, the Examiner states that no requirement has been made for achieving complete ablation of C2 GlcNAc transferase activity in order for the instant invention to be fully enabled. Instead, the Examiner contends that the "ability to achieve a desired phenotype in a null mutant is not representative of the ability to achieve this phenotype by administering inhibitors to an organism."

For reasons previously set forth in Applicants' amendments dated September 2, 2004, and February 17, 2005, Applicants believe that the pending claims are enabled by the specification under 35 U.S.C. § 112, first paragraph, and that the Examiner has not met the requisite burden for establishing an enablement rejection. However, to address the Examiner's contention regarding the predictability of using inhibitors in comparison to phenotypes seen in null mice, Applicants have submitted herewith the Declaration of Dr. Jamey Marth under 37 C.F.R. § 1.132 (also referred to herein as the "Marth Declaration"). As set forth hereinbelow, the Marth Declaration establishes that one of ordinary skill in the art would regard the specification's disclosure, including the disclosure of the null mutant C2 GlcNAc animal model, as reasonably providing enablement for the pending claims in view of the known art as of the effective filing date.

First, as of the effective filing date, it was well-known that gene target elimination in null mice is ***very*** predictive of the effects of using inhibitors that interact directly with the respective gene product *in vivo*. (Marth Declaration at ¶4.) Gene ablation had been routinely and extensively utilized to evaluate protein function *in vivo*. Indeed, because small molecule inhibition of protein function had been a well-established approach for drug development, the

pharmaceutical industry had relied on gene ablation studies, including mouse knockouts, to provide insight as to useful protein targets for therapeutic intervention. (*Id.* at ¶4.) In this regard, Applicants note that a comparison of top-selling drugs with data obtained from knockout mice show that there is an excellent correlation between phenotypes in null mice and known drug efficacy. (*Id.* at ¶4, citing Zambrowicz *et al.*, *Curr. Opin. Pharmacol.* 3:563-570, 2003 (further citing various pre-filing references).)

In view of the above, the skilled artisan reading the specification would readily accept that inhibition of C2 GlcNAc transferase protein *in vivo* would provide the claimed effect, *inter alia*, inhibition of an inflammatory response in a mammal. (Marth Declaration at ¶5.) As previously set forth in Applicants' amendment dated September 2, 2004, the following was known in the skilled artisan:

(a) C2 GlcNAc transferase is involved in the early steps of the biosynthesis of core 2 *O*-glycans in inflammatory cells (including neutrophils) and lymphocytes (*see id.* at page 4, lines 19-27);

(b) core 2 *O*-glycans in many cells comprise sialyl Lewis^X, an oligosaccharide ligand recognized by the selectin family of leukocyte adhesion molecules (*see id.* at page 4, lines 2-10, and Figure 1); and

(c) selectin receptors are known to be associated with a number of functions including leukocyte extravasation at cites of inflammation and lymphocyte trafficking in lymph nodes (*see id.* at page 4, lines 28 & 29.)

What was not known was whether C2 GlcNAc transferase modified leukocyte glycoproteins involved in extravasation of inflammatory cells or, in particular, whether inhibiting the activity of this enzyme would inhibit such extravasation. The studies set forth in the specification not only clearly established this *in vivo* effect of C2 GlcNAc transferase inhibition,

but identified this enzyme as a particularly advantageous target for specifically modulating the inflammatory response without affecting immune cell function. (*Id.* at ¶5.) As shown in the specification, using the null mutant mouse model, elimination of C2 GlcNAc transferase function *in vivo* results in inhibition of the extravasation of neutrophils and other inflammatory cells, while leaving lymphocyte trafficking and other immune functions relatively intact (*see* specification at page 18, lines 6-11; *see also* Marth Declaration at ¶5).

For the reasons above, and in light of the specification's teachings, those of skill in the art would readily accept that inhibitors of C2 GlcNAc transferase inhibitors could be used to achieve reduction of an inflammatory response in a mammal. (*Id.* at ¶6.) Thus, the pertinent question for evaluating enablement of the pending claims is "what was the state of the art with respect to *in vivo* inhibition of glycosyltransferases as of the specification's filing date?" In this regard, Applicants reiterate, as previously set forth in the previously filed amendments, that the art of glycosyltransferase inhibitors was well-advanced as of the effective filing date, and that glycosyltransferase inhibitors had a history of use *in vivo*. (*Id.* at ¶6.)

The Examiner does not refute Applicants' assertions regarding the state of the art of glycosyltransferase inhibitors. Instead, the Examiner states that there are "delivery issues" to address, and that while "in vitro assays do exist, they are not adequately predictive or correlative of the ability to provide for treatment effects in a subject without further experimentation." The Examiner also asserts that the use of C2 GlcNAc transferase inhibitors "for antiviral or antibacterial agents does not provide enablement for the treatment effects claimed." (Advisory Action dated March 22, 2005, at pages 2 & 3.)

With respect to "delivery issues" and the predictive value of *in vitro* assays for *in vivo* use, the only evidence offered by the Examiner as alleged support for this position is Lowe *et al.* (reference AI in Applicants' IDS). However, an examination of Lowe *et al.* in view of the knowledge in the art shows that this reference does not support the Examiner's position regarding delivery of gycosyltransferase inhibitors, nor the Examiner's position regarding the predictability of *in vivo* use of glycosyltransferase inhibitors based on *in vitro* assays. (*See* Marth Declaration at ¶7.)

As previously noted in Applicants' response dated February 17, 2005, the language cited by the Examiner relates to the use of inhibitors of the interaction of selectins and their carbohydrate ligands, ***not*** inhibitors of glycosyltransferases. (*Id.* at ¶7.) This is an important distinction in the present case. Therapeutic approaches based on the direct blocking of receptor-ligand interactions was relatively new, especially with respect to the use of smaller inhibitory molecules (as opposed to, *e.g.*, antibodies or soluble forms of receptors). In contrast, enzymes, including glycosyltransferases, have consistently proven to be very successful drug targets. In particular, the inhibition of enzyme activity via the use of molecules that interact directly with the enzyme protein was a well-established approach in the pharmaceutical industry. (*Id.* ¶7.)

Accordingly, those of skill in the art would ***not*** reasonably view Lowe *et al.* as indicating an "unpredictability of in vivo treatments for inflammation using the instantly claimed approach," as alleged by the Examiner (Office Action dated November 19, 2004, at page 5.) (Marth Declaration at ¶11.) As alleged support for the Examiner's interpretation of the relevance of Lowe *et al.*, the Examiner cites the following passage:

> Antibody blocking studies have been informative because these reagents bind with high affinity to their cognate antigens ... by contrast, the other types of inhibitory molecules are generally smaller, have intravascular half lives that are much shorter, or less well-defined, and may have lower affinities and/or specificities for the cognate receptor. Most interventional efforts have made use of acute inflammatory models that assess neutrophil recruitment, due to the lack of long-acting selectin blocking reagents, difficulties arranging continuous, long-term intravascular delivery of the available short acting inhibitors, and the paucity of information concerning the functional relevance of selectin-dependent leukocyte recruitment in chronic inflammatory conditions."

(Office Action dated 11/19/2004, at page 5 (citing Lowe *et al.*, at page 823).) Applicants will address the factors mentioned in the above-cited passage in view of the specification's disclosure and the pertinent knowledge in the art, particularly in view of the above-referenced distinction between inhibition of intracellular enzymes and extracellular receptor-ligand interactions.

First, as to the statement in Lowe *et al.* regarding a "paucity of information concerning the functional relevance of selectin-dependent leukocyte recruitment in chronic inflammatory conditions," Applicants note that the instant specification provides guidance in this regard. (Marth Declaration at ¶8.) The studies set forth in the specification demonstrate the functional relevance of a particular subset of selectin ligands modified by C2 GlcNAc transferase: using the null mutant mouse model, elimination of C2 GlcNAc transferase function *in vivo* results in inhibition of the extravasation of neutrophils and other inflammatory cells, while leaving lymphocyte trafficking and other immune functions relatively intact (*see* specification at page 18, lines 6-11; *see also* Marth Declaration at ¶8.) The skilled artisan reading the specification as of the filing date would readily accept the results of these studies as showing the functional relevance of certain selectin ligands, and of C2 GlcNAc transferase in particular, in inflammatory responses. (*Id.* at ¶8.)

Second, as to the statements in Lowe *et al.* regarding half-life and binding affinity, it is emphasized that these statements are made in the context of the intravascular use of small molecules for direct blocking of receptor-ligand interactions. (*See* Marth Declaration at ¶9.) As noted above, this was a relatively new therapeutic approach as of the effective filing date. The use of smaller molecules for blocking extracellular protein-protein interactions in the intravascular milieu presented new technical issues different than those traditionally encountered, and successfully addressed, with the use of smaller inhibitors for inhibition of enzymes intracellularly. The skilled artisan would not expect, *a priori*, the stability or localized concentrations of compounds used extracellularly in the intravascular space to be representative of the stability or localized concentrations of compounds designed and used to act intracellularly. Nor would the skilled artisan expect binding affinities or compound concentrations necessary to directly block receptor-ligand interactions to be representative of affinities or concentrations necessary to inhibit enzymatic activity. At least for these reasons, the skilled artisan would understand the compound pharmacokinetics and pharmacodynamics involved with the approach described in Lowe *et al.* to be significantly different than that involved with method as presently

claimed. (*Id.* at ¶9.) Therefore, the statements in Lowe *et al.* regarding half-life and binding affinities are essentially not relevant to enablement of the present invention.

Third, regarding specificities of inhibitors, as noted previously in Applicants' response dated 9/2/2004, the state of the art in making glycosyltransferase inhibitors was advanced at the time of the invention. (*Id.* at ¶9.) For example, analogs of glycosyltransferase substrates were routinely used to design inhibitors having specificity for the corresponding glycosyltransferase. Further, the skilled artisan would reasonably expect glycosyltransferase inhibitors with demonstrated specificity *in vitro* to retain such specificity *in vivo*. (*Id.* at ¶10.)

With respect to the Examiner's assertion that the use of C2 GlcNAc transferase inhibitors "for antiviral or antibacterial agents does not provide enablement for the treatment effects claimed," Applicants again note that these facts are relevant to show that, as of the filing date, such inhibitors had been used successfully *in vivo* for other indications. (*See id.* at ¶12.) It is not reasonable for the Examiner to dismiss these facts on the mere basis that they relate to a different therapeutic use. Indeed, the *in vivo* use of the C2 GlcNAc glysosyltransferase inhibitors for antiviral or antibacterial indications shows that issues relating to *in vivo* stability, binding affinity, and specificity of such inhibitors (as referenced in the Lowe *et al.* passage cited by the Examiner) had been successfully addressed by those skilled in the art before the filing date. (*See* Marth Declaration at ¶12.) That the present claims are directed to a different use – reducing an inflammatory response – does not prevent the relevance of these previous *in vivo* uses, particularly in view of (a) the specification's disclosure demonstrating reduction of an inflammatory response via genetic ablation of C2 GlcNAc transferase and (b) the understanding by those skilled in the art that *in vivo* effects observed in gene knockouts is predictive of effects obtained by *in vivo* inhibition of the gene product. Therefore, in light of the specification's disclosure and the previous successful *in vivo* use of C2 GlcNAc transferase inhibitors, the skilled artisan would readily accept that C2 GlcNAc transferase inhibitors would have *in vivo* efficacy in reducing an inflammatory response. (*See id.* at ¶12.)

As to Applicants' previous remarks regarding Exhibit B[1], the Examiner asserts that the "potential financial success of a clinical endeavor does not substitute for the experimentation required to determine the actual clinical viability of the claimed invention," and that "[m]any clinical approaches have failed, despite financial investments for them." Applicant note that whether a clinical approach "fails" is based on criteria established by the Food and Drug Administration (FDA). The criteria for FDA approval are different from the criteria for patentability. As stated in the MPEP, the Patent Office "must confine its review of patent applications to the statutory requirements of the patent law. Other agencies of the government have been assigned the responsibility of ensuring conformance to standards established by statute for the ... use, sale or distribution of drugs." MPEP § 2107.03 (V).

Further, Applicants reiterate, as discussed in the amendment filed 2/17/05, that Exhibit B shows that those skilled in the art recognized that use of glycosyltransferase inhibitors *in vivo* for the treatment of inflammation was not entirely unpredictable. (Marth Declaration at ¶13.) It is clear from the press release that GlycoDesign had developed inhibitors of C2 GlcNAc transferase that were a major part of the value obtained by Inflazyme's purchase of GlycoDesign for $12.8 million. As the first item identified as a rationale for the purchase is the fact that GlycoDesign has developed novel Core 2 inhibitors, at least some portion of the purchase price of the company can be attributed to the value placed on the C2 GlcNAc transferase inhibitors. (*Id.* at ¶13.) Moreover, Applicants note that an informed assessment of relative risks is a fundamental part of any determination to make a large financial investment in a company. For these reasons, Inflazyme's acquisition of GlycoDesign, and thus investment into Core 2 inhibitors, is relevant show that those of pertinent skill regarded *in vivo* use of such inhibitors as reasonably predictable in the art. (*See id.* at ¶13.)

For at least the reasons set forth above and reasons of record, claims 36-49 are enabled under 35 U.S.C. § 112, first paragraph. Withdrawal of the rejection is respectfully requested.

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[1] The Examiner also states that no Exhibit B was provided in Applicants' response dated 2/17/05. Applicants have therefore submitted herewith copy of Exhibit B ("Inflazyme enters into Agreement to Acquire GlycoDesign," April 2003).

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,

Dated: June 17, 2005 By: _____
Nicholas V. Sherbina
Reg. No. 54,443

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
Attachments
NVS/jms
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